IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff	)	
v.	)	C.A. No. 23-975 (RGA) (SRF)
LIQUIDIA TECHNOLOGIES, INC.,	)	
Defendant.	)	

PLAINTIFF'S OPENING POST-TRIAL BRIEF REGARDING INFRINGEMENT

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TABLE OF ABBREVIATIONS

’327 patent	U.S. Patent No. 11,826,327
6MWD	6 minute walk distance
Asserted Claims	Claims 1, 5, 6, 9, 14, 17
DPI	Dry powder inhaler
FDA	Food and Drug Administration
FVC	Forced vital capacity
Group 1	WHO Group 1 PH, pulmonary arterial hypertension
Group 3	WHO Group 3 PH, including PH-ILD and PH-COPD
INCREASE	Clinical trial conducted by UTC in patients with PH-ILD. Formally named *Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE*, ClinicalTrials.gov number NCT02630316
Liquidia	Liquidia Technologies, Inc.
Liquidia’s 505(b)(2) NDA	NDA 213005
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAH	Pulmonary arterial hypertension (Group 1)
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease
PI	Prescribing Information (*e.g.*, drug label)
RLD	Reference listed drug
UTC	United Therapeutics Corporation
USPTO	United States Patent and Trademark Office

'327 PATENT – ASSERTED CLAIMS

Claim	**Claim Limitation**
1[preamble]	A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising
1[a]	administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease
1[b]	an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof
1[c]	in a single administration event that comprises at least 6 micrograms per breath.
5	The method of claim 1, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.
6	The method of claim 1, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.
9	The method of claim 1, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.
11 (*not asserted*)	The method of claim 1, wherein said administering is performed by a pulsed inhalation device.
14	The method of claim 11, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.
17	The method of claim 1, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.

I. INTRODUCTION

The '327 patent claims methods of improving exercise capacity for patients with PH-ILD. Liquidia stipulated that it induces doctors and patients to directly infringe claims 1 and 14, and UTC established both direct and induced infringement of claims 5, 6, 9, and 17 at trial.

Doctors and patients will directly infringe the Asserted Claims when they use Yutrepia. PFF ¶¶ 7-14, 17-21. Liquidia's § 505(b)(2) NDA is not supported by any clinical trials of Yutrepia in PH-ILD. *Id.* ¶¶ 10-12, 14. Instead, Liquidia contends that Yutrepia is equivalent to Tyvaso and relies on UTC's "existing clinical efficacy and safety data for treprostinil (described in the Tyvaso PIs and peer-reviewed literature)"—*e.g.*, the results of UTC's INCREASE trial—to support its PH-ILD indication. *Id.* ¶¶ 10-14. The INCREASE data on which Liquidia relies makes clear that patients following the Yutrepia label are more likely than not to directly infringe.

Liquidia induces that infringement through its label and marketing materials for Yutrepia. Liquidia admits that it intends doctors and patients to follow its Yutrepia label. *Id.* ¶ 7. And Liquidia has been aware of the claims of the '327 patent since at least the day after they were allowed by the USPTO. *Id.* ¶¶ 15-16. Liquidia's only defense to infringement is that its label does not instruct doctors to measure the claimed improvements. But there is no "measurement" limitation in the claims, and measurement of every patient taking Yutrepia is not required to assess infringement because Liquidia relies on INCREASE to establish the performance of Yutrepia in PH-ILD patients. *Id.* ¶¶ 6-14, 17-21. There can be no real dispute that Liquidia induces infringement of the Asserted Claims where it represents that Yutrepia is "equivalent" to Tyvaso and INCREASE for purposes of FDA approval and commercial marketing.

II. STATEMENT OF FACTS

A statement of facts is provided in Plaintiff's Proposed Findings of Fact ("PFF").

III. LEGAL STANDARDS

Infringement is a question of fact, which UTC has the burden to prove "by a preponderance of the evidence," *i.e.*, more likely than not. *Eli Lilly & Co. v. Teva Parenteral Meds.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017). In a Hatch-Waxman case, under § 271(e)(2), the "infringement inquiry … is focused on the product that is likely to be sold following FDA approval… [b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the [NDA]'s description of the drug[.]" *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). Infringement is assessed "based on consideration of *all* the relevant evidence, including the ANDA filing, *other materials* submitted by the accused infringer to the FDA, *and other evidence* provided by the parties." *Id.* (emphasis added). A party is liable for infringement by others if it "actively induces infringement." 35 U.S.C. § 271(b); *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988). "Inducement requires that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010).

For method-of-treatment patents, an NDA applicant has "the requisite specific intent to induce infringement [when it] include[s] instructions in its proposed label that will cause at least some users to infringe the asserted method claims." *AstraZeneca LP*, 633 F.3d at 1060. "[T]he sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent[.]" *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011). Further, when all the relevant evidence "suggest[s] to treating clinicians that they can expect" a claimed "statistically significant" reduction, "and the fact that such a reduction will generally occur in their patients in clinical practice," courts have found induced infringement. *Amarin Pharma, Inc. v. Hikma Pharms. USA Inc.*, 449 F. Supp. 3d 967, 1002-1003 (D. Nev. 2020).

IV. YUTREPIA INFRINGES THE ASSERTED CLAIMS

Claim 1 recites a method of improving exercise capacity in PH-ILD patients by administering inhaled treprostinil. Dependent claim 14 requires administration with a DPI. Claims 5, 6, 9, and 17 recite a reduction in NT-proBNP, a reduction in exacerbations of the patient's ILD, an improvement in forced vital capacity ("FVC"), and an improvement in 6 minute walk distance ("6MWD"), respectively. These claims depend from independent claim 1 and narrow it to only those methods that provide the claimed improvements. The Yutrepia label, INCREASE trial results, and peer-reviewed literature—on which Liquidia relied—establish infringement of these claims by a preponderance of evidence.

Liquidia's contrary arguments fail. The claimed methods do not have a "measuring" step. All that is required is a showing that doctors and patients will administer the claimed drug at the claimed doses, and that this administration will, more likely than not, achieve the claimed improvements in NT-proBNP, ILD exacerbations, FVC, and 6MWD. UTC has met this standard.

A. Liquidia represents that Yutrepia will perform equivalent to Tyvaso.

Tyvaso is the RLD for Liquidia's § 505(b)(2) NDA, and Liquidia relies on UTC's data to establish Yutrepia's safety and efficacy. PFF ¶¶ 5, 10-11. That data includes the INCREASE trial, as "described in the Tyvaso PIs and peer-reviewed literature." *Id.* ¶ 10. For example, Section 14.2 of the Yutrepia label describes INCREASE in detail and reports that the recommended Yutrepia doses are "equivalent" to the doses of Tyvaso used in INCREASE. *Id.* ¶¶ 7-9, 11. Liquidia also represents that Yutrepia exhibits "comparable pharmacokinetics" to Tyvaso. *Id.* ¶ 13. Liquidia's handpicked expert advisor, Dr. Franck Rahaghi, concluded that Yutrepia would "inherit" the results of INCREASE along with Tyvaso's PH-ILD indication. *Id.* ¶ 14. Likewise, Liquidia's Chief Medical Officer, Dr. Rajeev Saggar, testified that Yutrepia would "meet or exceed" Tyvaso's performance in INCREASE. *Id.* ¶ 12. Liquidia's marketing materials to payors, doctors, and

patients also expressly rely on data from the INCREASE trial. *Id.* ¶¶ 12, 18.

Claims 5, 6, 9, and 17 reflect clinical benefits that were observed on a population basis in INCREASE when Tyvaso was administered to PH-ILD patients. *Id.* ¶ 6. By relying on INCREASE results that, in addition to being reported in the literature, are described in the '327 patent's specification, Liquidia has all but expressly conceded infringement.

B. Liquidia had knowledge of the '327 patent and what it claims.

Liquidia knew of the '327 patent and its claims before marketing Yutrepia for PH-ILD. *Id.* ¶¶ 15-16. Liquidia nonetheless markets Yutrepia for uses covered by the Asserted Claims. *Id.*

C. Liquidia infringes claims 1, 5, 6, 9, 14, and 17.

When doctors and patients follow the Yutrepia label to treat PH-ILD, they will directly infringe the Asserted Claims, and Liquidia actively instructs and encourages this infringement.

1. Liquidia infringes claims 1 and 14.

Liquidia stipulated to direct and induced infringement of claims 1 and 14. *Id.* ¶ 17.

2. Liquidia infringes claim 5.

Claim 5 depends from claim 1 and further requires that "said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering."

Direct Infringement: Doctors and patients will meet the NT-proBNP limitation of claim 5 by administering Yutrepia according to its label, which instructs how to achieve results "equivalent" to those obtained in INCREASE. *Id.* ¶¶ 7-11, 18. For example, Waxman 2021 (PTX-147) published the INCREASE trial results, including that, at 16 weeks, patients receiving inhaled treprostinil reduced their NT-proBNP levels by 1,850.30 pg/mL. PFF ¶ 18. Liquidia's Yutrepia marketing materials report these results *(id.)*, indicating that PH-ILD patients receiving Yutrepia are more likely than not to reduce their NT-proBNP plasma levels by at least 200 pg/mL. *Id.*

Induced Infringement: Liquidia's myriad representations that Yutrepia will perform equivalently to Tyvaso in INCREASE confirm that Liquidia markets Yutrepia with the knowledge that doctors and patients will infringe claim 5 when they follow the label. *Supra* § IV.A.; PFF ¶¶ 7-14, 18. That the NT-proBNP results from INCREASE are not expressly reported in the Yutrepia label does not excuse Liquidia's active inducement here, especially in view of the label's promise of "equivalent" performance to Tyvaso as well as Liquidia's explicit reliance on the peer-reviewed literature describing INCREASE in its representations to FDA and in its marketing materials. PFF ¶¶ 9-14, 18; *see also, e.g.*, *Intendis GMBH v. Glenmark Pharms. Ltd*., 117 F. Supp. 3d 549, 573 (D. Del. 2015), *aff'd sub nom. Intendis GMBH v. Glenmark Pharms. Inc., USA*, 822 F.3d 1355 (Fed. Cir. 2016) ("Defendants should not be permitted to liken their product to the claimed composition to support their bid for FDA approval, yet avoid the consequences of such a comparison for purposes of infringement."); *Bone Care Int'l, L.L.C. v. Roxane Labs., Inc.*, C.A. No. 09-285-GMS, 2012 WL 2126896, at *31 (D. Del. June 11, 2012) (defendants knew or should have known "based on the clinical trials and literature available" that administering the accused drug would result in claimed effects); *Allergan, Inc. v. Sandoz Inc.*, No. 6:11-CV-441, 2014 WL 12622277, at *10, *28 (E.D. Tex. Jan. 13, 2014), *aff'd*, 796 F.3d 1293 (Fed. Cir. 2015). Indeed, this Court rejected a similar argument from Liquidia in a prior litigation between the parties. *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 462-63 (D. Del. 2022), *aff'd*, 74 F.4th 1360 (Fed. Cir. 2023), and *vacated in part*, C.A. No. 20-755-RGA, 2024 WL 1328902 (D. Del. Mar. 28, 2024) ("The label, however, does not need to provide hemodynamic data to induce infringement. It just needs to instruct doctors and patients to administer a single event dose that is therapeutically effective."). Liquidia therefore instructs and encourages doctors and patients to administer Yutrepia in a manner that will practice claim 5. PFF ¶¶ 7-14, 18.

3. Liquidia infringes claim 6.

Claim 6 depends from claim 1 and further requires that "said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease."

Direct Infringement: Doctors and patients will meet the ILD exacerbations limitation of claim 6 by administering Yutrepia according to its label, which instructs how to achieve results "equivalent" to those obtained in INCREASE. *Id.* ¶¶ 7-11, 19. Waxman 2021 states that patients receiving inhaled treprostinil experienced a statistically significant reduction of ILD exacerbations at 16 weeks. *Id.* ¶ 19. Likewise, Liquidia's Yutrepia Provider Presentation cites Waxman 2021 to tell doctors that on inhaled treprostinil, "fewer patients had exacerbated underlying lung disease." *Id.* ¶ 19. Liquidia's own statements therefore establish that when Yutrepia is used according to its label across the treated population, doctors and patients will achieve a statistically significant reduction in exacerbations and are more likely than not to infringe claim 6. *Id.* ¶ 19.

Induced Infringement: Like claim 5, Liquidia's representations that Yutrepia will perform equivalently to Tyvaso in INCREASE establish that Liquidia markets Yutrepia with the knowledge that doctors and patients will infringe claim 6 when they follow the label. *Supra* §§ IV.A., IV.C.2.; PFF ¶¶ 7-14, 19. This is true even though reduced ILD exacerbations are not expressly discussed in the Yutrepia label because Liquidia represents (for purposes of FDA approval and marketing) that Yutrepia is equivalent to Tyvaso, citing peer-reviewed literature demonstrating the claimed reduction in exacerbations. PFF ¶¶ 9-14, 19; *Intendis*, 117 F. Supp. 3d at 573; *Bone Care*, 2012 WL 2126896, at *31; *Allergan*, 2014 WL 12622277, at *10, *28; *United Therapeutics*, 624 F. Supp. 3d at 462-63. Liquidia expects the population of PH-ILD patients receiving Yutrepia to experience a statistically significant reduction in exacerbations. PFF ¶¶ 9-14, 19. Liquidia therefore instructs and encourages doctors and patients to administer Yutrepia in a manner that will practice claim 6. PFF ¶¶ 7-14, 19; *see Amarin Pharma*, 449 F. Supp. 3d at 1003.

4. Liquidia infringes claim 9.

Claim 9 depends from claim 1 and further requires that "said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering."

Direct Infringement: Doctors and patients will meet the FVC limitation of claim 9 by administering Yutrepia according to its label, which instructs how to achieve results "equivalent" to those obtained in INCREASE. PFF ¶¶ 7-11, 20. Waxman 2021 states that patients administered inhaled treprostinil experienced a statistically significant improvement in FVC at weeks 8 and 16. *Id.* ¶ 20. Thus, doctors and patients using Yutrepia according to its label across the treated population are more likely than not to infringe claim 9. *Id.*

Induced Infringement: Like claims 5-6, Liquidia's representations that Yutrepia will perform equivalently to Tyvaso in INCREASE establish that Liquidia markets Yutrepia with the knowledge that doctors and patients will infringe claim 9 when they follow the label. *Supra* §§ IV.A., IV.C.2-3.; PFF ¶¶ 7-14, 20. It does not matter that FVC is not expressly discussed in the Yutrepia label because Liquidia is aware of the data in the literature demonstrating the claimed FVC improvement. PFF ¶¶ 9-14, 20; *Intendis*, 117 F. Supp. 3d at 573; *Bone Care*, 2012 WL 2126896, at *31; *Allergan*, 2014 WL 12622277, at *10, *28; *United Therapeutics*, 624 F. Supp. 3d at 462-63. The INCREASE results described in Waxman 2021 include a statistically significant improvement in FVC. PFF ¶¶ 20. Like claim 6, Liquidia expects that the population of patients receiving Yutrepia will experience the claimed FVC improvements. PFF ¶¶ 9-14, 20. Liquidia therefore instructs and encourages doctors and patients to administer Yutrepia in a manner that will practice claim 9. PFF ¶¶ 7-14, 20; *see also Amarin Pharma*, 449 F. Supp. 3d at 1003.

5. Liquidia infringes claim 17.

Claim 17 depends from claim 1 and further requires that "said administering increases a 6

minutes walk distance of the patient by at least 10 m after 8 weeks of the administering."

Direct Infringement: Doctors and patients will meet the 6MWD limitation of claim 17 by administering Yutrepia according to its label. PFF ¶¶ 7-11, 21. Section 14.2 of the Yutrepia label reports that, in INCREASE, PH-ILD patients receiving inhaled treprostinil experienced a 15 m increase in 6MWD after 8 weeks. *Id.* ¶ 21. Thus, doctors and patients using Yutrepia according to its label are more likely than not to infringe claim 17. *Id.*

Induced Infringement: As above, Liquidia's representations that Yutrepia will perform equivalently to Tyvaso in INCREASE confirm that Liquidia markets Yutrepia with the knowledge that doctors and patients will infringe claim 17 when they follow the label. *Supra* §§ IV.A., IV.C.2.; PFF ¶¶ 7-14, 21. Liquidia induces infringement because its "label and representations to the FDA confirm[ed] that its product meets the clinical limitations" of claim 17. *Allergan*, 2014 WL 12622277, at *28; *see also Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, 2023 WL 4175334, at *4-*9 (D. Del. June 26, 2023) ("the label induces infringement . . . regardless of whether the provider could be certain that [the drug] had been shown to increase survival."). Liquidia therefore instructs and encourages doctors and patients to administer Yutrepia in a manner that will practice claim 17. PFF ¶¶ 7-14, 21.

D. Claims 5, 6, 9 and 17 do not require a measurement step.

Liquidia and its expert, Dr. Channick, argue that claims 5, 6, 9, and 17 are not infringed because the Yutrepia label does not instruct healthcare providers to measure the endpoints recited in these claims. *See, e.g.*, Tr. 195:8-11. Not so. As Dr. Channick conceded, the plain language of the claims does not require "measurements" of NT-proBNP, FVC, ILD exacerbations, or 6MWD. PFF ¶ 6; Tr. 210:1-5. Dr. Channick further conceded that patients may experience the benefits recited in these claims—*e.g.*, a reduction in NT-proBNP—regardless of whether a measurement is taken. Tr. 209:3-7. There is no basis to read a measurement limitation into the claims here. *See*

Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc., 477 F. Supp. 3d 306, 354 (D. Del. 2020) ("[T]he Court understands the particle size limitation to describe a feature of the claimed invention, not a measurement requirement."). The relevant evidence establishes infringement, *see Abbott Labs.*, 300 F.3d at 1373, because doctors will prescribe Yutrepia and achieve the benefits recited in claims 5, 6, 9, and 17 and Liquidia knows from INCREASE that those results will more likely than not occur when Yutrepia is used according to its label. PFF ¶¶ 7-14, 17-21.

V. CONCLUSION

For the reasons above, Liquidia infringes claims 1, 5, 6, 9, 14, and 17 of the '327 patent. Plaintiff respectfully requests the Court enter judgment granting UTC its requested relief pursuant to 35 U.S.C. §§ 271(e)(2) and 271(e)(4), and any additional relief the Court deems just and proper.

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